Appl. No.: 10/810,296 Filed: March 27, 2004
Applicant/Inventor: Xing F. Wang, 16 Palm ST., Worcester, MA 01604-3844,
TEL: (774)-239-3884, Fax: (508)-831-0592

April 4, 2008

Primary Examiner Dr. John S. Brusca
Art Unit: 1631, Technical Center 1600,
Commissioner for Patents, USPTO,
P.O. Box 1450, Alexandria VA 22313-1450.

Dear Primary Examiner Dr. John,

Please find the enclosed Facsimile Transmission Cover Sheet of March 31, 2008. I have not received the fax as indicated in the Cover Sheet, resulting in the claim of the US patent application (Appl. No.: 10/810,296) not being changed or amended according to the fax.

Based on the enclosed *Office Action Summary* issued by Primary Examiner Dr. John S. Brusca on February 20, 2007, the examiner has acknowledged that the claims 1-10 are allowed; this application is in condition for allowance except for the following formal matters: Each of claims 11-18 is in improper multiple dependent form; the rejection of claims 1-18 under 35 U.S.C 101 has been withdrawn; and prosecution on the merits is closed in accordance with the practice under *Ex part Quayle*, 1935 C.D. 11, 453 O.G. 213. The improper multiple dependent form of claims 11-18 has been amended according to the enclosed *Interview Summary* issued by Primary Examiner Dr. Lori A. Clow on

August 20, 2007, wherein all dependent claims only reference or depend from one claim and the text of claim of the application is unchanged. The claim of the application is allowed after several words in claim 1 have been changed according to the Fax issued by Primary Examiner Dr. Lori A. Clow on December 5, 2007. Some words have been added into claim 2 according to the enclosed *Interview Summary* issued by Examiner Mr. Jason M. Sims on December 27, 2007, leading to the application in better condition for allowance. Based above several office actions, it is unnecessary to amend further the claim of the application after the text and form of the claim have been allowed by the two primary examiners of USPTO. Most nation patent offices including the International Bureau of international application do not allow further amendment to the claim once it is accepted by the examiner.

Please find the enclosed abstract of a review article published in Nature, 21 February 2008, Vol 451, 904-913, which is related to the US patent application. The latest review article in atherosclerosis research emphasizes that certain lipoproteins such as the low-density lipoprotein (LDL) and renin-angiotensin-aldosterone system, one of inflammation pathways, or C-reactive protein (CRP), one of inflammation markers, are important in the pathogenesis of atherosclerotic cardiovascular disease (ACD), and efforts to understand how risk factors such as high blood pressure, elevated LDL and CRP levels in human blood contribute to atherosclerotic diseases, are leading to new targets for therapy, as discussed in the abstract.

The US application is strongly supported by the latest review article because the contributions of elevated LDL and CRP levels in human blood, two main risk factors, to ACD have been integrated into the method of this invention by

means of the equations (1) and (3) in pages 3-4 of specification or equations (1) and (2) in pages 9-10 of claim of the application, and this method can be not only quantitatively to evaluate the contributions of various risk factors such as the high blood pressure, elevated LDL and CRP levels to ACD and the effects of various amounts of a risk factor to the disease but combine the contributions and effects, as indicated in examples 1-5 in pages 7-8 of the specification, which is significant improvements on available screening or diagnosing methods. This invention has provided some answers to fundamental questions in atherosclerosis, for example, how to understand and evaluate the contributions of risk factors to atherosclerotic diseases.

The US application has been over 4 years since filed March 27, 2004. The application as an international application has entered the examining stage in PCT national phases including EP, AU, CA, CN, JP, RU, IN, etc. I sincerely appreciate it if the notice of allowance is issued in this case soon.

Thank you for your consideration.

Sincerely,

Xingfa Wang

Xing F. Wang, Ph.D.
Applicant

Encl.: Fax cover sheet of 03/31/2008 (1 sheet), *Office Action Summary* of 02/20/2007 (3 sheets), *Interview Summary* of 08/20/2007 (1 sheet), *Interview Summary* of 12/27/2007 (1 sheet) and the abstract of review article (1 sheet).

FACSIMILE TRANSMISSION COVER SHEET

APPLICATION/CONTROL NUMBER: 10/810,296

Filed Date: March 27, 2004

DATE: March 31, 2008

TO: Techical Center 1600 via the Central PTO Fax Center, Fax: (571)-273-8300,

Examiner: Mr. Jason M. Sims, Art Unit: 1631,

TEL: (571)-272-7540, Fax: (571)-273-7540.

FROM: Xing F. Wang, Applicant/Inventor

TEL: (774)-239-3884, Fax: (508)-831-0592

MESSAGE:

Thanks for your call of March 31, 2008 regarding you are sending a fax to the applicant (Application No.: 10/810,296), then amendment to the claim of the application by the applicant according to the fax and returning the amended claim to the Technical Center 1600 via the Central PTO Fax Center (571-273-8300) tomorrow.

I have not received the fax. Please find the following applicant's contact information: Fax: (508)-831-0592, Phone: (774)-239-3884 and Email: xingfwang@gmail.com.

I appreciate it if I may receive the fax soon. Please contact the applicant if there is any question regarding above-mention matter. Thank you.

NUMBER of PAGES: 1 (INCLUDING THIS COVER SHEET)

Office Action Summary

Application No.	Applicant(s)	
10/810,296	WANG, XING FA	
Examiner	**Art Unit**	
Jason M. Sims	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 2 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 November 2006*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☒ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-10* is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☒ Claim(s) *11-18* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's After Final Amendment filed 11/27/2006 is acknowledged and has been entered.

Claims 1-18 are the current claims hereby under examination.

This application is in condition for allowance except for the following formal matters:

Claim Objections

Claims 11-18 are objected to under 37 CFR 1.75(c) as being in improper form because of improper multiple dependent claims. Each of claims 11-18 are in improper multiple dependent form. A claim can only reference one other claim or depend only from one other claim and claims referencing more than one claim or depending from more than claim are considered to be in improper multiple dependent form. For example, claim 11 references or depends from claim 1 and claims 2-10, which makes claim 11 an improper multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits.

Allowable Subject Matter

Claims 1-10 are allowed.

Response to Arguments

Applicant's arguments and amendment, filed 11/27/2006, with respect to the rejection under 35 U.S.C. 101 have been fully considered and are persuasive. The rejection of claims 1-18 under 35 U.S.C 101 has been withdrawn.

Conclusion

Prosecution on the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

A shortened statutory period for reply to this action is set to expire **TWO MONTHS** from the mailing date of this letter.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jason Sims, whose telephone number is (571)-272-7540.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Irem Yucel can be reached via telephone (571)-272-0781.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the Central PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The Central PTO Fax Center number is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

// Jason Sims //

John S. Brusca 20 February 2007

JOHN S. BRUSCA, PH.D
PRIMARY EXAMINER

Interview Summary	Application No.	Applicant(s)	
	10/810,296	WANG, XING FA	
	Examiner	Art Unit	
	Jason M. Sims	1631	

All participants (applicant, applicant's representative, PTO personnel):

(1) *Jason M. Sims*. (3)_____.

(2) *Xing Fa Wang*. (4)_____.

Date of Interview: *15 August 2007*.

Type: a)☒ Telephonic b)☐ Video Conference
c)☐ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☐ No.
If Yes, brief description: _____.

Claim(s) discussed: *1-18*.

Identification of prior art discussed: _____.

Agreement with respect to the claims f)☐ was reached. g)☒ was not reached. h)☐ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *Possible amendments to the claims, i.e. changing the dependencies of claims 3-10 to depend from each other, such as making claim 3 depend from claim 2, claim 4 depend from claim 3, etc. and then changing the claim dependencies of claims 12-16 to depend from claim 10 was discussed to overcome the new antecedent basis and multiple dependency problems to get the instant application in condition for allowance.*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

LORI A. CLOW, PH.D.
PRIMARY EXAMINER
Lori A. Clow
8/20/07

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.

Examiner's signature, if required

Interview Summary	Application No.	Applicant(s)	
	10/810,296	WANG, XING FA	
	Examiner	Art Unit	
	Jason M. Sims	1631	

All participants (applicant, applicant's representative, PTO personnel):

(1) *Jason M. Sims*. (3)_____.

(2) *Xing Fa Wang*. (4)_____.

Date of Interview: *12 December 2007*.

Type: a)☒ Telephonic b)☐ Video Conference
c)☐ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☐ No.
If Yes, brief description: _____.

Claim(s) discussed: *1 and 2*.

Identification of prior art discussed: _____.

Agreement with respect to the claims f)☒ was reached. g)☐ was not reached. h)☐ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *An incoming fax of proposed amendments was discussed with another agreement that the orginal proposed amendments presented by the office was agreed to by the applicant which placed the application in better condition for allowance*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.

Examiner's signature, if required

NATURE Vol 451 21 February 2008 doi:10.1038/nature06783

Translating molecular discoveries into new therapies for atherosclerosis

Daniel J. Rader[1] & Alan Daugherty[2]

Atherosclerosis is characterized by the thickening of the arterial wall and is the primary cause of coronary artery disease and cerebrovascular disease, two of the most common causes of illness and death worldwide. Clinical trials have confirmed that certain lipoproteins and the renin–angiotensin–aldosterone system are important in the pathogenesis of atherosclerotic cardiovascular disease, and that interventions targeted towards these are beneficial. Furthermore, efforts to understand how risk factors such as high blood pressure, dysregulated blood lipids and diabetes contribute to atherosclerotic disease, as well as to understand the molecular pathogenesis of atherosclerotic plaques, are leading to new targets for therapy.

During atherosclerosis, the arterial wall gradually thickens to form an atherosclerotic plaque, resulting in the narrowing of the lumen of the artery. Consequently, the amount of blood supplied to the organ is reduced, most commonly affecting the heart and the brain. Plaques can abruptly rupture, causing a blood clot and often myocardial infarction (heart attack) or stroke. Intensive study of the cellular and molecular mechanisms that underlie atherogenesis (that is, the formation of atherosclerotic plaques) and plaque rupture has led to a consensus view of these processes[1] (Fig. 1). Initiation and progression of the lesion are highly complex processes, and many aspects of atherogenesis remain incompletely understood. Furthermore, in most cases, mechanistic insights have yet to be translated into therapeutic approaches. In this review, we discuss the most exciting advances in atherosclerosis research since 2000, emphasizing new findings that have translational and therapeutic implications. For a review of earlier findings, see ref. 2. At present, the two main conceptual approaches to therapy for atherosclerosis are manipulation of plasma lipoprotein metabolism or cellular cholesterol metabolism, and manipulation of inflammatory processes. Here we discuss both approaches, focusing on how recent findings might lead to new types of therapy. We set the scene with a discussion of how new therapeutic targets are identified and validated and then finish by looking at how genome-wide association studies are rapidly altering the way in which atherosclerosis is understood and might be treated.

Identification of therapeutic targets in humans and mice

Perhaps the most convincing evidence for a potential therapeutic target is provided when a human genetic condition arising from simple mendelian genetics is found to be associated with altered risk of atherosclerotic disease. An example is homozygous familial hypercholesterolaemia, which is caused by mutations in the gene encoding the low-density lipoprotein (LDL) receptor. The observation that this disease is associated with markedly premature atherosclerosis led to an understanding that increased concentrations of LDL cholesterol in plasma can cause atherosclerosis. This observation also led to the general concept that intervening to increase LDL-receptor expression would reduce LDL concentrations and thus the risk of atherosclerosis. However, classic mendelian disorders are not associated with most genes of interest, and even when they are, the prevalence of these disorders is usually too low to provide strong evidence of an association with atherosclerosis. By examining extended families, linkage studies have identified loci that seem to be important determinants of premature coronary artery disease, but it has often been challenging to identify the specific genes that cause disease. One notable recent success was the identification of a mutation in the gene encoding LDL-receptor-related protein 6 (LRP6) in a large family as responsible for autosomal dominant premature coronary artery disease accompanied by features of the metabolic syndrome (which is a group of risk factors that are commonly associated with coronary artery disease, including hyperlipidaemia, hypertension and insulin resistance)[3]. 'Candidate genes' are frequently tested by genotyping single-nucleotide polymorphisms (SNPs) in large cohorts (or groups) of patients and examining whether particular SNPs are associated with atherosclerotic disease. Unfortunately, many of the published association studies have not been subjected to rigorous replication[4]. Most recently, genome-wide association studies have been used in an attempt to identify genes that are significantly associated with atherosclerotic disease and its risk factors (discussed later).

Studies of genetically modified mice are also commonly used to identify and validate potential therapeutic targets, as well as to investigate atherosclerotic disease mechanisms in detail. The bidirectional flow of information between mouse and human studies has been crucial for furthering knowledge of atherosclerosis, as well as for validating new therapeutic targets. However, the relevance of mouse studies for understanding the pathophysiology of atherosclerosis in humans needs to be carefully considered. There are important differences between mice and humans with respect to two of the main processes involved in atherogenesis: lipoprotein metabolism and inflammatory pathways. In addition, there are many inconsistencies between the various studies of atherosclerosis in mice, and the basis of these discrepancies is often unclear. Strain differences might, in part, be responsible; indeed, there can be substantial genetic variation between control and experimental mice even after extensive backcrossing of both into the same strain. A lack of standardization in measuring lesion size in mice might also contribute to these discrepancies. Furthermore, there is an increasing recognition that lesion composition, rather than size, determines the acute complications of atherosclerotic disease in humans. However, compositional analysis of lesions in mice is not routine or standardized, and the implications of differing lesion composition for disease

[1]Cardiovascular Institute and Institute for Translational Medicine and Therapeutics, University of Pennsylvania School of Medicine, 654 BRBII/III, 421 Curie Boulevard, Philadelphia, Pennsylvania 19104, USA. [2]Cardiovascular Research Center and Gill Heart Institute, University of Kentucky, Wethington Building, Room 521, Lexington, Kentucky 40536, USA.